Complete Summary

GUIDELINE TITLE

(1) Transfusion guidelines for neonates and older children. (2) Amendments and corrections to the transfusion guidelines for neonates and older children.

BIBLIOGRAPHIC SOURCE(S)

Boulton F, BCSH Transfusion Task Force. Amendments and corrections to the 'transfusion guidelines for neonates and older children'. London (UK): British Committee for Standards in Haematology (BCSH); 2005 Dec 7. 5 p. [9 references]

Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P, Burbin G, Duguid J, Boulton F, Cohen H, Smith N, McClelland DB, Rowley M, Turner G, British Committee for Standards in Haematology Transfusion Task Force: Writing Group. Transfusion guidelines for neonates and older children. Br J Haematol 2004 Feb;124(4):433-53. [113 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update – Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Fetal, neonatal, and infant conditions requiring blood or blood product transfusions

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Anesthesiology
Cardiology
Dentistry
Gastroenterology
Hematology
Infectious Diseases
Obstetrics and Gynecology
Oncology
Pediatrics
Surgery
Thoracic Surgery

INTENDED USERS

Clinical Laboratory Personnel
Dentists
Hospitals
Physicians

GUIDELINE OBJECTIVE(S)

To re-evaluate current transfusion practices, particularly evidence-based practices where they exist, and to update recommendations in existing guidelines in the light of developments in transfusion and clinical practice

TARGET POPULATION

Neonates and children in the United Kingdom who require blood or blood component transfusion(s)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Blood and blood component specifications
    - Donor specifications
    - Leukocyte depletion
    - Cytomegalovirus seronegativity
    - Irradiation
    - Plasma and platelet compatibility
    - Administration
    - Pretransfusion testing
    - Selection of blood components
2. Intrauterine transfusion
    - Red cell preparation specifications
    - Platelet preparation specifications
3. Neonatal transfusion
    - Exchange transfusion
    - Small volume transfusion
    - Blood component specifications and procedures
    - Special indications for blood products
4. Transfusion support for children with hemoglobinopathies
    - Red cell specifications for transfusion in thalassemia and sickle cell disease
5. Transfusion support for hemopoietic stem cell transplantation, aplastic anemia, and malignancies
    - Irradiation of blood products
    - Red cell transfusion in stem cell transplantation
    - Component specifications
6. Transfusion support for cardiac surgery, extracorporeal membrane oxygenation, and acquired coagulopathies
    - Pharmacological agents to reduce blood requirements
    - Cell salvage and bloodless surgery
    - Coagulation components for cardiac surgery
    - Irradiation for Di George's syndrome
    - Anticoagulation
7. Autologous transfusion, including autologous predeposit
8. Blood handling and administration to reduce risks of transfusion hazards

MAJOR OUTCOMES CONSIDERED

- Mortality and morbidity
- Duration of hospitalization

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials.

Ib Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

Grade A Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib).

Grade B Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels IIa, IIb, III).

Grade C Requires evidence obtained from the expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendation grades (**A-C**) and levels of evidence (**Ia-IV**) are defined at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC) and the British Committee for Standards in Haematology (BCSH): Since the initial publication of the original guidelines, the Transfusion Task Force has become aware that they contain several inconsistencies and errors. Furthermore, new information has become available. These have led to the release of an erratum containing amendments and corrections. Changes to the recommendations as a result of the erratum are labeled "2005 Addendum."

Blood and Blood Component Specification

General Recommendations (Fetuses, Neonates, Infants and Children)

Donors

Components for transfusion *in utero* or to children under 1 year of age must be prepared from blood donated by donors who have given at least one previous donation within the past 2 years, which was negative for all mandatory microbiological markers.

Leucocyte Depletion

All components other than granulocytes should be leucocyte depleted (not more than 5×10^6 leucocytes per unit) at the time of manufacture (**level IV evidence, grade C recommendation**).

Cytomegalovirus (CMV)

The 'Guidelines of the UK Transfusion Services' (The Stationary Office, 2002) state that blood transfused in the first year of life should be CMV seronegative. The evidence for this is still under review, so this advice holds for the present. Other authorities state that components that have been leucodepleted to ($<5 \times 10^6$/unit have a significant reduction in risk of CMV transmission (American Association of Blood Banks, 2000; Council of Europe, 2002: **level IIb evidence, grade A recommendation**).

Although the efficiency with which blood products in the UK are depleted of leucocytes is high, only a few products are directly tested for compliance with the specification. This means that there is no guarantee that an individual product has been sufficiently depleted, so that the use of products that are CMV seronegative is still recommended where CMV-free products are indicated. However, in an emergency and where seronegative blood components are not available, transfusion of leucodepleted components is an acceptable, although less desirable, alternative (American Association of Blood Banks, 2000; Ronghe et al., 2002; The Stationary Office, 2002).

Irradiation

Blood components should be irradiated prior to transfusion in line with the Guidelines published by the British Committee for Standards in Haematology, "Guidelines on gamma-irradiation of blood components" (1996) (see also Appendix 2 in the original guideline document).

It is essential to irradiate all red cell and platelet components (with the exception of frozen red cells) for:

1. Intrauterine transfusion (IUT) (**level III evidence, grade B recommendation**)
2. Exchange transfusion (ET) of red cells after IUT (**level III evidence, grade B recommendation**)

3. Top-up transfusion after IUT (**level III evidence, grade B recommendation**)
4. When the donation is from a first- or second-degree relative or a human leucocyte antigen (HLA)-selected donor (**level III evidence, grade B recommendation**)
5. When the child has proven or suspected immunodeficiency (**level III evidence, grade B recommendation**)
6. Other indications as listed in the British Committee for Standards in Haematology, "Guidelines on Gamma-Irradiation of Blood Components" (1996)

The component must be irradiated to a minimum dose of 25 gray (Gy). For IUT and large volume transfusion (e.g., ET), the component should be used within 24 hours of irradiation and within 5 days of donation (**level IV evidence, grade C recommendation**). Red cells for top-up transfusion may be irradiated at any time up to 14 days after collection, and thereafter stored for a further 14 days from irradiation (**level IV evidence, grade C recommendation**).

Platelets transfused *in utero* to treat alloimmune thrombocytopenia and platelet transfusions given after birth to infants who have received either red cells or platelets *in utero* should be irradiated. However, there is no need to irradiate other platelet transfusions in preterm or term infants, unless they are from first- or second-degree relatives (**level III evidence, grade B recommendation**).

All granulocytes should be irradiated for patients of any age and transfused as soon as possible after irradiation (**level III evidence, grade B recommendation**).

Plasma and Platelet Compatibility

Platelets should be ABO and RhD identical with the recipient. If this cannot be ensured, then compatible components lacking high titre anti-A or anti-B should be transfused to group A or B recipients. Group AB fresh frozen plasma (FFP), specifically for transfusion in the first year of life, may be given. For platelet and FFP transfusions, plasma compatibility should be ensured whenever possible. Both products contain enough red cell stroma to stimulate Rh immunization (**level IIb evidence, grade B recommendation** and **level IV evidence, grade B recommendation**). Therefore, RhD-negative girls for whom only RhD positive products are available should receive anti-D immunoglobulin. The dose should be 50 international units (IU) anti-D per unit of FFP (200 to 300 mL) or per 500 mL of platelets transfused, or 250 IU per adult therapeutic dose of platelets (about 250 to 350 mL, whether from a single aphaeresis donation or from a pack derived from a buffy coat pool from four donations). Components must not contain other clinically significant red cell antibodies.

2005 Addendum: Dose of anti-D prophylaxis in the event of RhD positive platelets being transfused to RhD negative children: The dose recommended is wrong and internally inconsistent. The correct dose is 250 IU which is enough to cover five successive adult therapeutic doses of RhD positive platelets over a period of up to six weeks. Nevertheless, if a unit of RhD positive platelets has been given and followed by anti-D prophylaxis, and if further treatment with platelet concentrates is required, RhD negative platelets are preferred and recommended.

2005 Addendum: Selection of FFP according to RhD status: The recommendation above also states that there is enough red cell stroma in FFP (as well as in platelet concentrates) to stimulate RhD immunization. This is in contrast to the recommendations in the FFP Guidelines (see the National Guideline Clearinghouse (NGC) summary of the British Committee for Standards in Haematology (BCSH) Guidelines for the Use of Fresh Frozen Plasma, Cryoprecipitate and Cryosupernatant). A preliminary report indicates that the red cell stroma and microparticles residue in FFP is minimal, making negligible the risk of RhD alloimmunization to susceptible persons. (This is not the case for platelet concentrates.) The Task Force therefore endorses the recommendations in the FFP Guidelines, which are that the RhD status of FFP is not significant, so that RhD negative recipients can receive RhD positive FFP without the need for post-transfusion anti-D prophylaxis. The Task Force also notes that the UK Blood Safety and Quality Regulations 2005 continue to require that packs of FFP be labelled according to the donor's RhD status.

Administration

All components should be transfused through a standard blood giving set with a screen filter (170 to 200 microns) or an alternative system incorporating the same filtration. Where small volumes are drawn into a syringe an appropriate filter must be used. Microaggregate filters (40 microns) are not required for leucodepleted components.

Pretransfusion Testing for Neonates and Infants Within the First Four Postnatal Months

Wherever possible, samples from both mother and infant should be obtained for initial ABO and RhD group determination. Investigations on the maternal sample:

- ABO and RhD group
- Screen for the presence of atypical red cell antibodies

Investigations on the infant sample:

- ABO and RhD. ABO by cell group only, repeated on same sample if no historical result (a reverse group would detect passive maternal antibodies)
- Direct antiglobulin test (DAT) performed on the neonate's red cells

  2005 Addendum: Pre-transfusion testing for neonates and infants within the first four post-natal months: It should be realised that babies of unsensitised RhD negative mothers who have received antenatal prophylaxis with anti-D may be born with a positive direct antiglobulin test (DAT). This test should therefore only be performed on the cord blood if the mother has additional red cell allo-antibodies or as an investigation into haemolytic disease of the newborn, for example if the baby is jaundiced or anaemic. This issue is also being addressed by antenatal guidelines currently in preparation.

- In the absence of maternal serum, screen infant's serum for atypical antibodies by an indirect antiglobulin technique (IAT)

A positive DAT on the neonate's red cells or an atypical red cell antibody in maternal or neonatal serum suggests possible haemolytic disease of the newborn (HDN). In such cases, special serological procedures will be necessary to allow selection of appropriate blood (**level IV evidence, grade C recommendation**).

Selection of Blood Component

Components should be

- Of the neonate's own ABO and RhD group, or an alternative compatible ABO and RhD group
- Compatible with any ABO or atypical red cell antibody present in the maternal or neonatal plasma
- An electronic cross-match may not select blood that is compatible with maternally derived ABO antibodies in the neonate's plasma. Therefore, it may not be appropriate to include neonatal samples in electronic cross-match protocols unless an appropriate algorithm has been created. ABO identical adult blood transfused to an infant with maternal anti-A or anti-B may haemolyse even if the pretransfusion DAT is negative, due to stronger ABO antigen expression on adult cells (see section "ABO Haemolytic Disease of the Newborn" below and in the original guideline document; **level IV evidence, grade C recommendation**).
- Small volume transfusions can be given repeatedly over the first 4 months of life without further serological testing, provided that there are no atypical maternal red cell antibodies in the maternal/infant serum, and the infant's DAT is negative when first tested.
- If either the antibody screen and the DAT (or both) are positive, serological investigation or full compatibility testing will be necessary.

Infants rarely produce atypical red cell antibodies other than following repeated large volume transfusion and (possibly) the use of blood from donations collected up to 5 days before transfusion. It is only under these circumstances that repeat antibody screening of the recipient is advised (**level IIb evidence, grade B recommendation**). After the postnatal age of 4 months, compatibility tests should be conducted in accordance with national guidelines for pretransfusion testing in adult practice (British Standards in Haematology, "Guidelines for Pre-Transfusion Compatibility Procedures," 1996, "Chapman et al., Guidelines for Compatibility in Blood Transfusion Laboratories," 2004) (see table "Choice of ABO Group for Blood Products for Administration to Children" below).

Table: Choice of ABO Group for Blood Products for Administration to Children

Patient's ABO Group	**ABO Group of Blood Product to Be Transfused**		
	Red Cells	**Platelets**	**FFP***
O			

Patient's ABO Group	ABO Group of Blood Product to Be Transfused		
	Red Cells	Platelets	FFP*
First choice	O	O	O
Second choice	–	A or B	A or B or AB
A			
First choice	A	A	A
Second choice	O	B** ***	AB
Third choice	–	O**	B**
B			
First choice	B	B** ***	B
Second choice	O	A**	AB
Third choice	–	O**	A**
AB			
First choice	AB	AB***	AB
Second choice	A or B	A** or B** ***	A**
Third choice	O**	O**	B**
*Group O fresh frozen plasma (FFP) should only be given to patients of group O. Although group AB FFP can be given to people of any ABO blood group, supplies are usually limited.			
**Components which test negatively for 'high titre' anti-A and/or anti-B should be selected. The use of group O platelets for non-O patients should be avoided as much as possible.			
***Platelet concentrates of group B or of group AB may not be available.			

2005 Addendum: Selection of blood products according to ABO blood group (Table, above): Since publication of the original guideline, the UK Serious Hazards of Blood Transfusion (SHOT) scheme has reported two incidences of haemolysis after platelet concentrates of group O were transfused to non-group O children. Also, the International Forum on transfusion of apheresis platelets and ABO blood groups ("Transfusion," 2005) recommends that group O platelets should be avoided unless other contingencies such as human leucocyte antigen (HLA) or human platelet-specific alloantigen (HPA) restrictions, or CMV status, make only group O platelets available. Hence, Table 1 of the 2004 original guideline document is amended and replaced by the Table, above. The Task Force feels that this is particularly important. They also comment that there is no standard method for determining what constitutes 'high titres' of ABO antibody in blood donations and, as stated in the 'Guidelines for the Blood Transfusion Services in the UK' (available at www.transfusionguidelines.org.uk), "Components from group O donors with 'low titres' of anti-A, anti-B, and/or anti-A,B can cause intravascular haemolysis in non-group O recipients if given in sufficiently large volumes". The Task Force is aware of work to standardise this approach for the UK which, if successful, should reduce the incidence of unexpected haemolysis due to ABO antibodies. However, some normal individuals, mostly of group O, have plasma with ABO antibodies which although highly active clinically are in relatively low titres and may escape detection by dilution tests in vitro. Therefore, recipients who are not group O will remain vulnerable to ABO-related haemolysis following the administration of group O platelet concentrates suspended in plasma from such donors.

Intrauterine Transfusion

Indications and Aims

Intrauterine transfusions are usually administered only on specialized units. Intrauterine red cell transfusion is indicated to correct fetal anaemia caused by red cell alloimmunization (most important antigen-RhD followed by Rhc and K) or, less commonly, for fetal parvovirus infection. Intrauterine platelet transfusions are indicated to correct fetal thrombocytopenia caused by platelet alloimmunization. The aims of IUT are (i) to prevent or treat fetal hydrops before the fetus can be delivered and (ii) to enable the pregnancy to advance to a gestational age that will ensure survival of the neonate (in practice, up to 36 to 37 weeks) with as few invasive procedures as possible (because of the risk of fetal loss). This is achieved by (i) starting the transfusion programme as late as safely possible but before hydrops develops and (ii) maximizing the intervals between transfusions, by transfusing as large a volume of red cells as is considered safe. Cell counting should be available close to fetal sampling or transfusion to provide an immediate haematocrit/haemoglobin or platelet count.

Component and Procedure Specification

(See Table II of the original guideline document)

Red Cells Preparations

Red cells preparations for IUT should

- Be group O (low titre haemolysin) or ABO identical with the fetus (if known) and RhD negative. K-negative blood is recommended to reduce additional maternal alloimmunization risks. In exceptional cases, e.g., for haemolysis because of maternal anti-c, it may be necessary to give RhD positive, c-negative blood
- Be IAT-cross-match compatible with maternal serum and negative for the relevant antigen(s) determined by maternal antibody status
- Be <5 days old and in citrate phosphate dextrose (CPD) anticoagulant
- Be CMV seronegative
- Be irradiated as above (see "Irradiation" above)
- Have a haematocrit (packed cell volume, [PCV]) between 0.70 and 0.85

2005 Addendum: Haematocrit of blood for intrauterine transfusion: The original 2004 guideline recommended that the red cell preparation for IUT should have a haematocrit of up to but not more than 0.75. Surveys have indicated that most UK blood centres often prepare such materials with a higher haematocrit. Furthermore the Council of Europe Guidelines recommends that the haematocrit be between 0.70 and 0.85, while the UK Blood Services' Guideline simply states that the haematocrit not be below 0.70. The Transfusion Task Force therefore has amended the recommendation to be in line with the Council of Europe, so that the haematocrit should be between 0.70 and 0.85.

- Not be transfused straight from 4 degrees C storage. As no specifically designed warming systems exist for the small volume of blood used for IUT, any active warming must be carried out with great care and the blood product not exposed to temperatures higher than 30 degrees C. Active warming may not be necessary if the infusion is conducted carefully and at an appropriate rate (see below)
- Be in a volume calculated from the formula of (Rodeck and Deans, 1999):

$$\frac{\text{Desired PCV - Fetal PCV}}{\text{Donor PCV - Desired PCV}} \text{ X Fetoplacental BV}$$

- where BV is blood volume
- Be transfused at a rate of 5 to 10 mL/minute

Platelet Preparations

Platelet preparations for IUT should

- Be group O RhD negative and test negatively for high-titre anti-A or anti-B (i.e., have a low titre haemolysin) or group specific/compatible with maternal antibody
- Be human platelet-specific alloantigen (HPA) compatible with maternal antibody
- Preferably be collected by aphaeresis. A platelet concentrate derived from whole blood donations is less preferred
- Be irradiated as above (see "Irradiation" above)
- Be concentrated to a platelet count of at least 2000×10^9/l
- Be warmed, if warmed at all, with extreme care. As the ambient temperature for storing platelet concentrates is 22 degrees C, and as the recommended rate of infusion (see below) is slower than that for red cells, active warming may not be needed. If it is conducted, it should not be beyond 30 degrees C
- Be in a volume calculated from the formula

$$\frac{\text{Desired platelet increment}}{\text{Platelet count of concentrate}} \text{ X Fetoplacental BV}$$

- Be transfused at a rate of 1 to 5 mL/min (transfused more slowly than red cells because of the increased risk of fetal circulatory stasis and asystole).

Compatible platelets should be available at the time of diagnostic fetal sampling for alloimmune thrombocytopenia, even if the primary purpose is not that of transfusion, because in the presence of severe fetal thrombocytopenia, fetal haemorrhage can be prevented by platelet transfusion.

Teflon-coated needles should be used because they are considered to allow samples of fetal blood which give more accurate cell counts (Welch et al., 1995: **level IIb evidence, grade B recommendation**).

Neonatal Transfusion

Exchange Transfusion

Indication and Aims

Exchange transfusion (ET) may be used to manage severe anaemia at birth, particularly in the presence of heart failure, and to treat severe hyperbilirubinaemia, usually caused by HDN. In the treatment of haemolytic disease of the newborn (HDN), the aim is to remove both the antibody-coated red cells and the excess bilirubin. Controversial indications such as metabolic disease, septicaemia and disseminated intravascular coagulation (DIC) have not been subjected to adequate clinical evaluation.

ET is a specialist procedure associated with a potential for serious adverse events. As such, it should be undertaken only by staff who are experienced in the procedure.

Principles

While there is, as yet, no consensus amongst neonatologists, plasma-reduced red cells with a haematocrit of 0.50–0.60 should be suitable for ET for both hyper-bilirubinaemia and severe anaemia (**level IV evidence, grade C recommendation**).

'Correction' of pH to physiological levels by the addition of buffer solutions is not indicated.

Component and Procedure Specifications

Red cells for ET should

- Be group O or ABO compatible with maternal and neonatal plasma, RhD negative (or RhD identical with neonate)
- Be negative for any red cell antigens to which the mother has antibodies
- Be IAT-cross-match compatible with maternal plasma
- Be 5 days old or less (to ensure optimal red cell function and low supernatant potassium levels)
- Be collected into CPD anticoagulant
- Be CMV seronegative
- Be irradiated and transfused within 24 hours of irradiation. Irradiation is essential if the infant has had a previous IUT and is recommended for all ETs

(see "Irradiation" above and Appendix 2 of the original guideline document). Irradiation for ET in absence of IUT is not essential if this would lead to clinically significant delay

- Have a haematocrit of 0.50 to 0.60
- Not be transfused straight from 4 degrees C storage. If it is decided to warm the product prior to transfusion, extreme care must be taken to avoid over-heating
- Volume transfused is usually 80 to 160 mL/kg for a term infant and 100 to 200 mL/kg for a preterm infant (i.e., 1 to 2 × blood volume) depending on the clinical indication (see Table II of the original guideline document; **all level IV evidence, grade C recommendation**).

ABO Haemolytic Disease of the Newborn

If transfused with blood of their own group, group A or B babies who have maternal anti-A or anti-B in their plasma may convert to DAT positivity and develop haemolysis. This is due to the increased expression of A and B antigens on adult cells of those groups. Group O blood, compatible with the maternal plasma, should be used for transfusion (**level IV evidence, grade C recommendation**).

If an ET is required in ABO HDN, this should be with group O red cells with low titre plasma anti-A and anti-B, or with group O red cells suspended in AB plasma (**level IV evidence, grade C recommendation**).

Small Volume Transfusion

See Tables II and III of the original guideline document for component volumes to be transfused to children and neonates and suggested transfusion thresholds for infants under 4 months of age.

Dedicating aliquots from a single donation of red cells (or aphaeresis platelets) to allow sequential transfusions from the same donor for neonates and small children who are likely to be repeatedly transfused is considered good practice. These must be transfused within the normal shelf-life (currently 35 days for red cells in additive solution, 5 days for platelets).

Guidelines for Administration of Red Cells

It is impossible to produce clear evidence-based criteria for the administration of red cells in the neonatal period. However, clinicians who transfuse according to agreed local guidelines give fewer transfusions and it is recommended that local transfusion protocols be established in all neonatal units (Ross et al, 1989: **level Ib evidence, grade A recommendation**).

Table III of the original guideline document gives proposals for neonatal red cell audit criteria. These are not 'transfusion triggers' per se, but represent standards against which individual nurseries can assess the appropriateness of their local transfusion policies (**level IV evidence, grade C recommendation**).

<u>Anaemia of Prematurity</u>

The aim of a top-up transfusion is to restore or maintain adequate tissue oxygen delivery without a marked increase in oxygen consumption (Alverson et al., 1988; Maier et al., 2000).

Oxygen Dependency

Neonates with severe pulmonary disease are thought to benefit from a higher haemoglobin or haematocrit (0.40), which allows oxygen delivery to be optimized in the presence of underlying respiratory insufficiency. There is now some evidence that systemic oxygen delivery is improved and oxygen consumption decreased in infants with oxygen-dependent bronchopulmonary dysplasia by maintaining a haematocrit more than 0.40 (Alverson et al., 1988: **level Ib evidence, grade A recommendation**).

Erythropoietin

Recombinant human erythropoietin (EPO) may reduce red cell transfusion requirements in neonates. However, its effect appears to be relatively modest and does not reduce transfusion requirements within the first 2 weeks of life, when sick neonates are most transfusion dependent because of frequent blood sampling. The optimal dose, timing and nutritional support required during EPO therapy has yet to be defined and currently the routine use of EPO in this patient group is not recommended as similar reductions in blood use can probably be achieved by institution of appropriate transfusion protocols (Maier et al., 1994, 1998; Shannon et al., 1995; Franz & Pohlandt, 2001: **level IIb evidence, grade B recommendation**).

Fresh Frozen Plasma

FFP should never be used as a simple volume replacement and it is not clearly superior to crystalloids or colloids in the management of neonatal hypotension. Routine administration to preterm infants to try to prevent periventricular haemorrhage (PVH) has been shown to confer no benefit and should therefore be avoided ("Randomised trial," 1996: **level IIb evidence, grade A recommendation**).

Neonates with a significant coagulopathy (e.g., prothrombin time [PT] or activated partial thromboplastin time [APTT] ratio >1.5) and significant risk of bleeding (e.g., preterm and/or intubated, previous PVH) or who are about to undergo an invasive procedure should receive FFP at a dose of about 15 mL/kg (**level IV evidence, grade C recommendation**).

Note: Polycythaemia may lead the plasma of a citrated sample to be overcitrated and dilute. Correction of the prolonged coagulation screen is unpredictable and this should therefore be rechecked following administration.

FFP should not be used to treat polycythaemia unless there is a co-existent coagulopathy. FFP has not been proven to have clinical benefit when given to septic patients in an attempt to improve immune function. Indeed the use of this component in sepsis may increase mortality, although the reason for this is not clear (Busund, Straume, & Revhaug, 1993).

Platelets

In the absence of randomized, controlled trials in thrombocytopenic preterm infants, recommendations for platelet transfusion must be made on the basis of clinical experience. Term infants are unlikely to bleed if the platelet count is maintained above 20×10^9/l but in small, preterm babies a higher threshold is generally recommended, particularly during the first few days when the risk of PVH is highest or if there is a co-existent coagulopathy (**level IV evidence, grade C recommendation**). In neonatal alloimmune thrombocytopenia, HPA-compatible platelets will be required, in addition to high dose intravenous immunoglobulin (see "2005 Addendum" below). In these patients, a minimum platelet count of 30×10^9/l is recommended because the HPA antibody can impair platelet function (**level IV evidence, grade C recommendation**) (see also British Committee for Standards in Haematology, "Guidelines for the Use of Platelet Transfusion," 2003; Table III of the original guideline document).

2005 Addendum: Neonatal allo-immune thrombocytopenia – HPA-type of transfused platelets: The Task Force now recommends that if HPA1a5b platelets are not available to treat babies with NAIT, platelet concentrates selected randomly, whatever their HPA status (if known), should be given.

Granulocyte Concentrate

Production and Storage

Granulocyte concentrates obtained by centrifugation of refrigerated whole blood units are of poor function and generally yield inadequate doses. They should be obtained by centrifugation leucapheresis.

Granulocytes should be stored in the same donor's citrate-anticoagulated plasma at room temperature and kept unagitated. They should be administered within 12 hours of preparation. Storage for more than 8 to 12 hours is associated with marked loss of function. Close liaison with the blood transfusion centre is essential to ensure that mandatory virology testing can be completed in time to allow infusion of a potentially effective component.

Indications for Granulocyte Transfusion

Neonates with severe sepsis, who are deteriorating despite antibiotics and who have severe neutropenia for more than 24 hours may benefit from granulocyte transfusion. However, these patients may also respond to the administration of granulocyte colony-stimulating factor (G-CSF) and currently it is not clear which of these approaches is more effective.

Component Specification and Procedure

Red Cells for Small Volume Transfusion

Red cells for small volume transfusion should

- Be ABO compatible with mother and infant, and infant's RhD group (or RhD negative) (see table above for ABO group selection of all components)
- Be IAT compatible with maternal plasma (if available) or neonate's plasma for first transfusion (and subsequent transfusions up to four postnatal months if atypical maternal antibodies present)
- Be 35 days old or less [if in saline, adenine, glucose and mannitol solution (SAG-M) or similar additive system] or 28 days old or less (if in CPD) (**level Ia evidence, grade A recommendation**)
- Have a haematocrit of 0.50 to 0.70
- Be irradiated if appropriate (see "Irradiation" above)
- Usually be infused in a volume of 10 to 20 mL/kg
- Be aliquoted donations (pedi-pack) from a single unit dedicated to one infant (**level Ib evidence, grade B recommendation**)

Platelets for Neonatal Transfusion

Platelets for neonatal transfusion should

- Be ABO identical or compatible (see TABLE above): RhD identical or compatible
- Be HPA compatible in infants with alloimmune thrombocytopenia
- Be produced by standard techniques without further concentration
- Be irradiated if appropriate
- Usually be infused in a volume of 10 to 20 mL/kg (see Table II of the original guideline document)

Fresh Frozen Plasma for Neonatal Transfusion

FFP for neonatal transfusion should

- Be group AB, or compatible with recipient's ABO red cell antigens (see table above)
- Usually be infused in a volume of 10 to 20 mL/kg (see Table II of the original guideline document)

Virus inactivated plasma (VIP) should be used for the treatment of patients with inherited coagulation deficiencies where no pathogen-inactivated (PI) factor concentrate is available (United Kingdom Haemophilia Centre Directors' Organisation, 1997). In other children the decision to use a PI-FFP rests with individual clinicians.

Granulocytes: Dose and Duration of Therapy

The suggested dose is 1 to 2 × 10^9 granulocytes/kg (Englefriet, Reesink, & Klein, 2000: **level IIa evidence, grade B recommendation**). The component must be ABO compatible with the recipient (as it is heavily contaminated with red cells), RhD compatible (RhD negative for RhD negative females) and irradiated to a minimum dose of 25 Gy prior to administration. It should also be CMV seronegative if appropriate (see "Cytomegalovirus" above and "Transfusion Support for Haemopoietic SCT, Aplastic Anaemia and Malignancies, General Points" Below). The optimal duration of therapy is unclear but two or more daily infusions of an appropriate dose have been associated with improved outcome (Englefriet, Reesin, & Klein, 2000).

Special Indications for Blood Products

Partial Exchange Transfusion for Polycythaemia

In the presence of symptomatic hyperviscosity, partial ET to reduce the haematocrit to 0.55 or below may be beneficial (**level IV evidence, grade C recommendation**). Crystalloid is an effective exchange fluid and controlled studies show no additional benefit when FFP or albumin is employed (**level Ib evidence, grade A recommendation**). However, if the baby is hypoalbuminaemic then dilutional exchange performed with 4.5% albumin will benefit the hypoalbuminaemia. The formula for calculating the volume (in mL) is:

$$\frac{\text{Blood volume X Observed PCV} - \text{Desired PCV}}{\text{Observed PCV}}$$

Use of Albumin, Synthetic Colloids and Crystalloids

Severe hypoalbuminaemia may be associated with marked peripheral oedema and respiratory distress and hypoalbuminaemic infants have an increased mortality. However, it is not clear that this relationship is causal, and there is no evidence that simply increasing the albumin level by albumin infusion positively affects the outcome.

Transfusion in Necrotizing Enterocolitis

It is recommended that patients with necrotizing enterocolitis (NEC) be transfused with red cells in SAG-M as this is relatively plasma-free. Platelets, FFP and/or cryoprecipitate should only be administered when clearly indicated. Any patient with NEC who develops haemolysis, should be investigated to determine the cause of this. This should include a lectin test to look for T-activation. Where it is felt that T-activation is the likely cause, then an ET may be necessary. There is support but no consensus for routine provision of 'low-titre anti-T' plasma and platelet product for patients with T-activation. Access to these rare products is limited.

Transfusion Support for Children with Haemoglobinopathies

General Considerations

Children with Haemoglobinopathies

All children on regular transfusions should be vaccinated against hepatitis B as early as possible. Those on chronic transfusion therapy, particularly those with haemoglobinopathies, but also those with congenital dyserythropoietic anaemia, aplastic anaemia and other bone marrow failure syndromes, should have an extended red cell phenotype (Rh and Kell; see also "Red Cell Specifications for Transfusion in Thalassaemia and SCD" below for sickle cell disease [SCD]) performed prior to, or as soon as possible after, commencing regular transfusions.

Reviews of the literature addressing allogeneic red cell and plasma transfusions in children have been published recently (Hume, 1996; Hume, Kronick, & Blanchette, 1997: **level Ib evidence, grade A recommendation**).

Volume of Blood for Top-Up (Standard) Transfusion

A commonly used formula for determining the volume of packed red cells for top-up (standard) transfusion in infants and children is:

Desired haemoglobin (Hb) (g/dL) − Actual Hb × Weight (kg) × 3.

The recommended rate of transfusion of red cell products is about 5 mL/kg per hour.

Acceptable ABO Group

See table "Choice of ABO Group for Blood Products for Administration to Children" above.

Indications and Aims

Thalassaemia Major

By definition all patients with thalassaemia major are transfusion dependent. Transfusion therapy is determined by the degree of anaemia and evidence of failure to thrive. Most children start transfusion when their haemoglobin concentration falls below 6 g/dL.

Aim: current guidelines (Cazzola et al., 1997: **level IIb, grade B recommendation**; Prati, 2000: **level IV evidence, grade C recommendation**) and the new Thalassaemia International Federation guidelines (Olivieri, 1999: **level IIa evidence, grade B recommendation**) recommend:

- Maintaining an *average* Hb of 12 g/dL
- Maintaining a *pretransfusion* Hb of 9 to 10 g/dL
- That transfusion should prevent marrow hyperplasia, skeletal changes and organomegaly
- Red cell requirements should be adjusted to accommodate growth and hypersplenism considered if red cell requirements increase unexpectedly
- Iron chelation therapy should be considered after 10 transfusions and started once the ferritin is more than 1000 micrograms per liter (if possible starting after 2 years of age) (Olivieri, 1999: **level IIa evidence, grade B recommendation**)

Sickle Cell Disease

Red cell transfusion in children with SCD (Ohene-Frempong, 2001; Telen, 2001) should not be routine but reserved for specific indications (**level Ib evidence, grade A recommendation**; see Table IV of the original guideline document).

When to use simple additive or top-up transfusion in SCD:

- Splenic or hepatic sequestration
- Aplastic crisis

Aim: To raise the haemoglobin concentration to the child's normal steady state (the haemoglobin should never be raised acutely to >10 g/dl, as this is likely to cause an increase in blood viscosity).

When to use ET in SCD (Schmalzer et al., 1987; Emre et al., 1995):

- Acute chest syndrome (**level IV evidence, grade C recommendation**). The aim is to reduce sickling and increase oxygen carriage without an increase in viscosity
- Stroke; priapism (see Table II of the original guideline document)

When to use hypertransfusion in SCD:

- Patients on regular transfusions to prevent recurrence of stroke (Pegelow et al., 1995: **level IIa evidence, grade B recommendation**)
- Of probable value to delay or prevent deterioration in end organ failure (e.g., chronic sickle lung)
- To prevent the development of stroke in children with SCD with Doppler and/or magnetic resonance imaging evidence of cerebro-vascular infarction/haemorrhage in the absence of clinical evidence of stroke (Miller, Jensen, & Rao, 1992: **level III evidence, grade C recommendation**; Adams et al., 1998: **level Ib evidence, grade A recommendation**)

Aim: To maintain the percentage of sickle haemoglobin (HbS) below 25% and the Hb between 100 and 14.5 g/dL. After 3 years a less intensive regimen maintaining the HbS at ≤50% may be sufficient for stroke prevention (Adams et al., 1998: **level Ib evidence, grade A recommendation**; Cohen et al., 1992: **level Ib evidence, grade B recommendation**).

Transfusion and surgery in SCD (Riddington & Williamson, 2001*).* It is standard practice in Europe and North America to transfuse children with SCD preoperatively despite lack of evidence. Based on observational studies (Koshy et al., 1995: **level Ib evidence, grade A recommendation**; Griffin & Buchanan, 1993: **level III evidence, grade B recommendation**) and one large randomized controlled study (Vichinsky et al., 1995: **level IIb evidence, grade B recommendation**):

- Top-up transfusion aiming for Hb 8 to 10 g/dL is as effective as ET and may be safer (Vichinsky et al., 1995: **level IIb evidence, grade B recommendation**)
- Minor and straightforward procedures (e.g., tonsillectomy, possibly cholecystectomy) can be safely undertaken without transfusion in most patients (Roberts-Harewood et al., 1997: **level III evidence, grade B recommendation**; Hatley et al., 1995: **level IV evidence, grade C recommendation**; Haberkern et al., 1997: **level Ib evidence, grade A recommendation**)
- Transfusion should be performed preoperatively for major procedures (e.g., hip or knee replacement, organ transplantation, eye surgery and considered for major abdominal surgery)

Exchange transfusion in SCD. Reducing the percentage of HbS in the blood of children in the acute situation to 20% or less requires a total exchange of 1.5 to twice their blood volume. When conducted manually this generally requires two to three procedures; but automated cell separation enables the exchange to be completed in one procedure.

Normal saline (not FFP or albumin) should be used as volume replacement at the beginning of the exchange prior to starting venesection to avoid dropping the circulating blood volume. ET may also be used to minimize iron overload in patients on regular transfusions (Cohen et al., 1992: **level IIb evidence, grade B recommendation**; Kim et al., 1994: **level IIb evidence, grade B recommendation**).

Red Cell Specification for Transfusion in Thalassaemia and SCD

(See also Table IV of the original guideline document)

Such patients should be extensively phenotyped for red cell antigens (Rh, K in thalassaemia; Rh K, Fy, Jk and MNS in SCD) before the first transfusion. This is to facilitate selection of appropriate products should they become necessary, and to minimize alloimmunization (Singer et al., 2000: **level IIb evidence, grade B recommendation**; Olujohungbe et al., 2001: **level III evidence, grade B recommendation**; Davies & Roberts-Harewood, 1997: **level IIa evidence, grade B recommendation**; Vichinsky et al., 2001: **level IIb evidence, grade B recommendation**). All S− and s− patients should be typed for U.

Red cell preparations for thalassaemia and SCD should

- Be ABO compatible (see table "Choice of ABO Group for Blood Products for Administration to Children" above)
- Be matched for Rh and K antigens (two-third of antibodies are in the Rh or K system and may be transient leading to a risk of delayed haemolytic transfusion reaction). The Ro (cDe) genotype is common in people of Afro-Caribbean origin: all individuals phenotypically Ro must be transfused with C-negative and E-negative blood. This can be provided from rr or Ro red cells; Ro is to be preferred if available as rr blood should, whenever possible, be reserved for D-negative patients
- Be 35 days old or less (if collected into SAG-M or similar additive system) or 28 days old or less (if collected into CPD); there is no overall advantage in using 'neocytes' for top-up transfusion (Collins et al., 1994; Spanos et al., 1996: **level IIb evidence, grade B recommendation**)
- Be tested for HbS prior to transfusion, as sickle-trait positive red cells should not be transfused

  2005 Addendum: Whereas this is a legitimate requirement for children (and adults) with sickle-cell disease, the Task Force wishes to clarify that this is not necessarily the case for children with a thalassaemia syndrome unless it be co-inherited with HbS.

- Be CMV negative if appropriate (see "Cytomegalovirus" above)

<u>Transfusion Support for Haemopoietic Stem Cell Transplantation (SCT), Aplastic Anaemia and Malignancies</u>

General Points

All children with aplastic anaemia, or who are being treated with high-dose chemotherapy and/or radiotherapy may become candidates for SCT. While some clinicians consider components that have been depleted to $<5 \times 10^6$ leucocytes per unit to be CMV-safe (see "Cytomegalovirus" above), not all SCT centres agree (see "Transfusion Support for Children with Haemoglobinopathies" above).

Irradiation of blood products is not necessary in children receiving chemotherapy for leukaemia or solid tumours with the exceptions listed in "Irradiation of Blood Products" below.

Indications for Transfusion

Red Cells

There are no controlled trials upon which to base decisions about red cell transfusions in this group of children. The decision therefore depends on clinical judgement, taking into account the child's general condition, the presence or absence of bleeding and whether or not there are signs of haematological recovery. For children with aplasia, red cell transfusions are usually reserved for symptomatic patients with Hb values <7 g/dL, as sensitization to large numbers of transfusions reduces the chance of a successful outcome. The introduction of universal leucocyte depletion in the UK appears likely to reduce this risk (Saarinen, Koskimies, & Myllyla, 1993; Williamson, 2000: **level III evidence, grade B recommendation; level Ib evidence, grade A recommendation**).

Platelets

In the absence of evidence-based guidelines for children, the table below reflects current recommended practice in children (Hume, 1996: **level IIb evidence, grade B recommendation**); Cahill & Lilleyman, 1998: **level IV evidence, grade C recommendation**; Ancliff & Machin, 1998: **level IV evidence, grade C recommendation**; Howard, Gajjar, & Ribeiro, 2000: **level III evidence, grade B recommendation**) and in adults ("Platelet transfusion therapy," 1987; Norfolk et al., 1998: **level IV evidence, grade C recommendations**; Wandt et al., 1998: **level IIa, grade B recommendation**), as well as the recent evidence-based guidelines produced by the American Society of Clinical Oncology which almost exclusively refers to studies in adults (Schiffer et al., 2001: **level Ib evidence, grade A recommendation**). In children with aplasia, a restrictive policy with platelet transfusion is safe for long-term management (Sagmeister, Oec, & Gmur, 1999: **level IV evidence, grade C recommendation**). However, children with aplastic anaemia during and following treatment with anti-lymphocyte globulin (ALG) in particular may require intensive platelet support. In contrast, some paediatricians are prepared to conduct follow-up lumbar punctures on children with counts as low as 20×10^9/l, having not experienced unduly high adverse effects.

Note: This recommendation differs from that in the recent Guidelines for the transfusion of platelets (British Committee for Standards in Haematology, "Guidelines for the Use of Platelet Transfusions," 2003), where the recommended threshold value is 50×10^9/l.

Table: Indications for Prophylactic Platelet Transfusion in Children with Thrombocytopenia as a Result of Reduced Production

Platelet count <10×10^9/l
Platelet count <20×10^9/l and one or more of the following
Severe mucositis
Disseminated intravascular coagulation (DIC)
Anticoagulant therapy
Platelets likely to fall <10×10^9/l before next evaluation
Risk of bleeding due to a local tumour infiltration
Platelet count 20–40 $\times 10^9$/l and one or more of the following
DIC in association with induction therapy for leukaemia
Extreme hyperleucocytosis
Prior to lumbar puncture or central venous line insertion

Using data from Hume (1996)

Granulocytes

There is no evidence to support the use of prophylactic granulocyte transfusions (Engelfriet et al., 2000: **level IV evidence, grade C recommendation**). Empirical data from some but not all studies (**level Ib evidence, grade A recommendation**) support their use in the setting of severe bacterial or fungal infection in neutropenic children (Englefriet, Reesink, & Klein, 2000: **level IV evidence, grade C recommendation**; Price et al., 2000: **level IV evidence, grade C recommendation**; Bhatia et al., 1994: **level III evidence, grade B recommendation**) and, after SCT, to reduce the incidence of infection (Hubel et al., 2001: **level III evidence, grade B evidence**), but they increase the risk of platelet refractoriness, and few SCT centres use them. Therapeutic granulocyte transfusions may have a role in patients with congenital neutrophil dysfunction or severe neutropenia who are suffering from severe bacterial infection, are clinically deteriorating and unlikely to recover in a week despite maximal supportive care, including cytokines (Price et al., 2000: **level IV evidence, grade C recommendation**). Patients who are likely to receive a sibling/parent allograft should not receive granulocytes from family donors (see "Granulocyte Concentrate, Production and Storage" above and in the original guideline document). The efficacy of granulocytes collected from G-CSF-stimulated donors may be superior and is currently being evaluated (Price et al., 2000; Hubel et al., 2001: **level IV evidence, grade C recommendations**).

Component Specification

Irradiation of Blood Products

Irradiation of blood products (see Appendix 2 of the original guideline document)

- For 2 weeks before all types of SCT and during conditioning for all types of SCT whichever is longer
- In allogeneic SCT, irradiation should continue indefinitely
- In autologous SCT, irradiation should continue for 3 months post-SCT (6 months if total body irradiation (total body irradiation (TBI) given)
- For SCT in children with severe combined immunodeficiency (SCID), irradiation should continue for at least a year following SCT or until normal immune function has been achieved
- For 7 days prior to harvesting of autologous bone marrow or peripheral blood stem cells (PBSCs)
- For children with Hodgkin's disease during treatment and thereafter the susceptibility to transfusion-associated graft versus host disease (GvHD) is now considered to be life-long (Williamson, 1998: **level IV evidence, grade C recommendation**)
- During treatment with fludarabine and for at least 2 years or until full recovery of cellular immune function (Williamson et al., 1996; Williamson, 1998: **level IV evidence, grade C recommendation**)
- Where blood products from relatives are being used

Red Cell Transfusion in SCT: Specification

For patients who have received an ABO compatible SCT red cell components for transfusion should

- Be ABO group compatible (see table "Choice of ABO Group for Blood Products for Administration to Children" above)
- Be RhD compatible (Note Bene: After SCT, RhD negative red cells are given if the patient is RhD negative and/or the donor is RhD negative)
- Be leucocyte depleted ($<5 \times 10^6$/unit) at the time of manufacture
- CMV negative if appropriate (see "Cytomegalovirus" above)
- Be irradiated to a minimum of 25 Gy if SCT imminent (see "Irradiation of Blood Products" above)

For patients who have received an ABO incompatible SCT, red cell components for transfusion should

- Be group O (irrespective of the ABO group of SCT donor) until ABO antibodies to the donor ABO type are undetectable and the DAT is negative; thereafter red cells of the donor group are given

ABO incompatibility between the patient and SCT donor may be major, minor or both. In major incompatibility, the recipient has antibodies to the SCT donor red cells; in minor incompatibility, the SCT preparation from the donor has antibodies to recipient cells; in both major and minor incompatibility, the recipient's plasma contains antibodies to the donor's cells and the donor plasma contains antibodies to the recipient's cells (e.g., recipient group B and SCT donor group A). However, selection of group O red cells for transfusion following an ABO incompatible SCT (SCT donor group A or B; patient group O) is straightforward, as O red cells in SAGM contain only small quantities of plasma. However, if a group A or B SCT shows relatively slow engraftment of red cells and anti-A or anti-B antibodies are slow to disappear, group O preparations from donors who are negative for high-titre anti-A,B or suspended in saline, may be preferred (see Section "ABO Haemolytic Disease of the Newborn" above and in the original guideline document).

Platelets: Specification

- ABO compatible where possible (see table "Choice of ABO Group for Blood Products for Administration to Children" above): in view of the risk of haemolysis where there is major ABO incompatibility (Duguid et al., 1999: **level IV evidence, grade C recommendation**).
- After an ABO incompatible SCT; platelets of the recipient's ABO group should be given until there is conversion to the donor ABO group and ABO antibodies to the donor ABO group are undetectable. Thereafter give donor group.
- Rh-D compatible: RhD negative girls must receive RhD-negative platelets in view of the risk of sensitization by contaminating red cells; RhD-negative platelets are also recommended for RhD-negative boys wherever possible.
- After SCT, RhD negative platelets are given if the patient is RhD negative and/or the donor is RhD negative.
- CMV negative if appropriate (see "General Points" under "Transfusion Support for Haemopoietic SCT, Aplastic Anaemia and Malignancies" above).
- Irradiated to a minimum of 25 Gy if SCT imminent (see "Irradiation of Blood Products" above).
- Recommended volume of platelet concentrate is 10 to 20 mL/kg for children under 15 kg and an aphaeresis unit for children over 15 kg.

Granulocytes

- ABO compatible
- RhD compatible (RhD negative girls must receive RhD negative granulocytes).
- CMV negative if appropriate (see "Cytomegalovirus" above).
- Irradiated to a minimum of 25 Gy for all recipients.

Fresh Frozen Plasma after ABO Incompatible SCT

After SCT from a major or a minor ABO mismatch, FFP of group AB should be given.

Components for Bone Marrow Donors

Healthy children who act as bone marrow donors for their sibling(s) usually require blood transfusion to cover blood lost during the procedure. In older children (over 25 kg and over 8 years old) autologous blood donation should be considered around 2 weeks prior to marrow/PBSC donation. Allogeneic blood transfused to the donor during the bone marrow harvest should be extensively phenotyped (Rh, K, Fy, Jk and MNS), irradiated and CMV-safe (see "Children with Haemoglobinopathies" above).

Transfusion Support for Cardiac Surgery, ECMO and Acquired Coagulopathies

Cardiac Surgery

Many children are iron deficient; pre-operative assessment should therefore include iron status.

Red Cells for Cardiac Surgery

A number of factors influence practice.

- There are some evidence that blood losses may be less when fresh blood (<48 hours old) is transfused (Mohr et al., 1988; Manno et al., 1991; Chambers, Cohen, & Davis, 1996), but only in very small children (under 2 years old) undergoing complex procedures. The benefit of fresh whole blood in cardiac surgery cannot be considered proven (Hershey & Glas, 1992).
- Infants having bypass surgery are effectively undergoing ET. For infants, it is reasonable to apply the same specifications as would be used in ET, i.e., red cells <5 days of age and not collected into optimal additive solutions, because of theoretical concerns about toxicity of the additive solution (**grade C recommendation**).

  2005 Addendum: Despite these theoretical concerns, there is no direct evidence against using red cells in additive solutions such as SAG-M for neonatal cardiac surgery, and many UK centres do so without apparent problems. A recent prospective randomized trial comparing whole blood with reconstituted blood for 200 infants undergoing cardiac surgery shows apparent safety of mannitol and adenine in this situation (Mou et al., 2004). The reconstituted blood contained optimal additive solutions, and the patient group that received it had a better outcome than the group that received fresh whole blood, with a shorter stay in intensive care and decreased perioperative fluid overload. Moreover there was no significant difference in the number requiring renal support therapy. Neonates (under 28 days old) constituted 39% of the study group, and there was no difference after subgroup analysis by patient age comparing those older than 28 days with those who were younger. In view of the current concerns in the UK over transfusion transmission of Variant Creutzfeldt-Jakob Disease (vCJD), and as plasma is a possible source of vCJD prion in infected persons (Gregori, et al., 2004), it is important to consider any implications of the significantly greater plasma volume in CPD blood components when compared to SAG-M red cell components. Hence, SAG-M red cell preparations may carry a significantly lower risk than CPD preparations of transmitting vCJD although this cannot at present be ascertained directly. This lower theoretical risk of vCJD transmission by SAG-M red cells has to be balanced with the possible but unproven risk of the additives in SAG-M, also taking into account the apparent safety of blood in these additives in neonatal cardiac surgery. In this context the Task Force recommends that paediatric cardiac centres already using SAG-M blood should continue to do so and that those using CPD should consider switching to SAG-M.

- There is no evidence to suggest that the transfusion of blood collected in additive solutions is associated with detriment in children older than 6 months (**grade C recommendation**).

- Older blood can be used for those older than 1 year, although units <10 days old should be provided whenever possible to cover the intraoperative and immediate postoperative periods when large volumes may be given quickly (**grade C recommendation**).
- The choice of fluid for bypass circuit priming (colloid and red cells, whole blood, crystalloid) is partly determined by the size of the patient, the volume of the extracorporeal circuit and the starting haemoglobin concentration.

Pharmacological Agents to Reduce Blood Requirements

- Desmopressin (DDAVP) in children undergoing cardiac surgery (Reynolds et al., 1993). This has been shown to be of no benefit in reducing blood loss (**level Ib evidence**).
- High dose aprotinin appears to be of value in reducing blood loss only in patients undergoing complex primary procedures (e.g., transposition of the great arteries) or in re-do procedures (Boldt et al., 1993; Carrel et al., 1998; Miller et al., 1998: **level II evidence, grade B recommendation**).
- Low dose aprotinin (e.g., 500,000 units in pump prime only) is ineffective.
- Tranexamic acid has been shown to reduce blood loss in children with cyanosis undergoing cardiac surgery and in those undergoing repeat procedures. A variety of dose regimes have been used, but a dose of 10 mg/kg followed by an infusion of 1 mg/kg per hour in adults produces an appropriate inhibitory level of tranexamic acid throughout the procedure (Fiechtner et al., 2001: **level III evidence, grade B recommendation**).
- Vitamin K deficiency is common in cyanotic infants preoperatively and should be corrected (Urban et al, 1984: **level IIb evidence, grade B recommendation**).

Cell Salvage and 'Bloodless' Surgery

- Cell salvage procedures should be encouraged. Red cells salvaged from the extracorporeal circuit at the end of bypass are safe and effective in reducing homologous transfusion (Friesen, Tornabene, & Coleman, 1993: **level III evidence, grade B recommendation**).
- Bloodless cardiac surgery using isovolaemic haemodilution and bloodless priming of the extracorporeal circuit has been carried out successfully in the children of Jehovah's Witnesses (Stein et al., 1991: **level III evidence, grade B recommendation**).
- Evidence is available from adult practice (Spence et al., 1992) to support acceptance of a lower postoperative Hb level of 7 g/dL (**level III evidence**), which should also be appropriate in children with good postoperative cardiac function. There is no evidence to suggest any benefit from attempting to maintain a postoperative Hb concentration within the normal range (**grade B recommendation**).

Cold-Reacting Antibodies

Cold-reacting antibodies are of no clinical significance, even in patients who will be rendered hypothermic, and therefore do not require to be detected on antibody screens.

Coagulation Components for Cardiac Surgery

Bypass procedures induce a complex haemostatic defect, which has been well reviewed (Bevan, 1999: **level IV evidence**). Blood loss is higher in complex and 're-do' procedures and in children <1 year of age. Reduction in the size of the bypass circuit can significantly reduce FFP and platelet requirements (De Somer et al., 1996: **level III evidence, grade B recommendation**).

- The routine use of FFP is of no proven benefit in cardiac surgery. It offers no proven advantage unless there are documented derangements of coagulation after correction of excess heparinization. There is no place for 'formula' use of FFP (Unpublished observations: **level IV evidence, grade C recommendation**).
- Neonates in particular may have significantly low coagulation factors prior to bypass, which are then lowered further by dilution (Kern et al., 1992; Chan et al., 1997: **level IV evidence**).
- Excess protamine has been identified as an important and controllable cause of excessive bleeding (DeLaria et al., 1994: **level IIa evidence**).
- Platelet transfusions may be useful for thrombocytopenic bleeding or where platelet function is thought to be impaired.
- Topical thrombin/fibrin glues are effective in reducing suture line bleeding. If products incorporating aprotinin are used then it should be borne in mind that these patients may mount an immune response similar to those receiving intravenous aprotinin, which may cause reactions at the time of subsequent exposure.

Irradiation for Di George's Syndrome

(See Appendix 2 of the original guideline document.)

It is increasingly recognized that infants with a variety of congenital cardiac lesions have lesions of chromosome 22, i.e., are variants of Di George's syndrome. Dysmorphic infants with truncus or interrupted aortic arch who do not have all the features of Di George's syndrome and who need cardiac surgery should have irradiated cellular procedures until the syndrome has been excluded (**grade C recommendation**).

Extra Corporeal Membrane Oxygenation (ECMO)

During this highly specialized respiratory support, children are anticoagulated with heparin and require regular monitoring of coagulation parameters and platelet count.

- The combination of coagulopathy from the primary illness, the haemostatic defects associated with ECMO and haemodilution contribute to a high risk of intracranial haemorrhage.
- Following the initial 'coating' prime with albumin, priming with whole blood, packed red cells or packed cells and FFP may be indicated, particularly in very small babies and in those with a pre-existing coagulopathy.
- Blood should be as fresh as possible, and not more than 5 days old, in order to minimize the risk of hyperkalaemia.
- Whole blood or semi-packed red cells will contain a significant amount of relatively fresh plasma containing useful levels of all factors other than factor VIII and factor V.

- Red cells in additive solution are not advised for priming in view of the concerns about the possible toxicity of the constituents.
- Platelet transfusions should be given to maintain the platelet count above 100 $\times 10^9$/l and FFP given to manage excessive bleeding caused by documented coagulation factor deficiency.
- The fibrinogen level should be maintained above 0.8 to 1.0 g/l with cryoprecipitate 5 mL/kg.
- Antithrombin levels may be very low, and at least one group recommends antithrombin infusion to keep the levels adequate for heparin function (Urlesberger et al., 1996).
- A normal haematocrit (of around 0.45) has been associated with increased risk of clotting in the circuit and increased donor exposure, which may be reduced by lowering the haematocrit to about 0.35 (Griffin et al., 1992: **level Ib evidence**). However, the optimal haematocrit has not been determined.

Congenital and Acquired Coagulopathies

Congenital Coagulopathies

Congenital bleeding disorders are rare, but important to recognize in the bleeding infant.

- Where an infant presents unexpectedly with a bleeding diatheses requiring urgent treatment an adequate blood sample must be obtained for immediate testing prior to infusion of any blood product.
- If treatment cannot be delayed until the results of specific tests are available, virus-inactivated plasma (VIP) sourced from non-UK plasma may be given. A dose of 20 mL/kg should result in a rise of about 20% in coagulation factor levels.
- FFP is not optimal therapy for the more common severe coagulopathies, and is not sufficient for a baby with severe haemophilia A or B

Acquired Coagulopathies

The important acquired coagulopathies in infants and small children are:

- Vitamin K deficiency
- DIC
- Liver disease – liver failure
- Anticoagulant reversal

<u>Vitamin K deficiency</u> (Baglin, 1998; Sutor et al., 1999; unpublished observations).

Vitamin K is required for normal function of factors of II, VII, IX and X. Regimens for prevention and treatment of vitamin K deficiency have recently been published with the evidence base (**level IV evidence**).

- In the child with a coagulopathy caused by vitamin K deficiency without bleeding, intravenous vitamin K treatment is sufficient.
- The response to systemic vitamin K is rapid (within 30 to 120 minutes).

- In the presence of bleeding it is advisable to give, along with vitamin K, either FFP 10 to 20 mL/kg (preferably a VIP and sourced from non-UK plasma if age appropriate), or an intermediate purity factor IX concentrate ('prothrombin complex concentrate' [PCC]), which contains factors II, IX and X. If such a concentrate is used, consideration should be given to vaccinating the child/baby against hepatitis B.
- Factor IX concentrate ('PCC') used in this way has been shown to be effective for bleeding because of warfarin excess in adults, but there are no data in children with vitamin K deficiency to guide dosage (**level IV evidence, grade C recommendation**).
- It is important to repeat coagulation tests regularly over 24 to 48 hours to ensure correction is complete.

Disseminated Intravascular Coagulation

- The neonate is particularly vulnerable to the onset of DIC, perhaps because of the relative immaturity of the liver.
- While the primary aim should be to correct the underlying cause, FFP at a dose of 10 to 15 mL/kg, preferably pathogen-inactivated and sourced from non-UK plasma if the patient is of appropriate age, is indicated unless the coagulopathy is mild (coagulation times $<1.5 \times$ control) and the child is haemostatic.
- Cryoprecipitate at a dose of 5 mL/kg is indicated if the fibrinogen falls acutely to less than 0.8 to 1.0 g/l.
- Heat-treated pooled fibrinogen concentrates are at present unlicensed and not available in doses suitable for neonates.
- Platelet concentrates are indicated for significant thrombocytopenia (see Table III of the original guideline document).
- DIC needs to be monitored frequently to guide appropriate blood product therapy.

Liver Disease

- Severe liver failure is usually accompanied by profound coagulation derangements, including hypo-fibrinogenaemia.
- These children will need blood product support with cryoprecipitate (if the fibrinogen is less than 0.8 to 1.0 g/l) and FFP, until the liver recovers or the child has a liver transplant.
- Lesser degrees of coagulation derangement in hepatic dysfunction may require no coagulation support unless invasive procedures are required.
- Liver units tend to be guided by the international normalized ratio (INR) and consider liver biopsy to be safe if the INR is <1.4 or the PT up to 4 seconds longer than the upper limit of the normal range. APTT and thrombin time are not normally relevant for decision making (McGill et al., 1990: **level IV evidence, grade C recommendation**).
- The response to FFP in liver disease is unpredictable and repeat coagulation testing should be carried out immediately following completion of the infusion. The merits of continuous FFP administration (e.g., 5 mL/kg per hour) versus intermittent boluses have not been addressed.
- A platelet count of at least 50×10^9/l is recommended for liver biopsy (Grant & Neuberger, 1999), although a count of at least 70×10^9/l may be preferable, particularly in the presence of an underlying coagulopathy.

- An important factor in bleeding risk may be the experience of the operator (Gilmore et al., 1995: **level III evidence**).

Anticoagulation in Children, and Its Reversal

- There are few published data on anticoagulation in children.
- A single centre review of 319 children (Streif et al., 1999) includes useful guidelines for dosing strategies, noting that infants who have had a Fontan procedure require a smaller dose of warfarin to achieve the target INR than other children (**level III evidence, grade C recommendation**).
- Guidelines on oral anticoagulation produced by the British Committee for Standards in Haematology are based entirely on adult data, and there are no trials demonstrating that these guidelines are optimal for children ("Guidelines on oral," 1998: **level IV evidence**).
- The principles of anticoagulant reversal in children are the same as for adults: for children with an INR >8.0 without bleeding, satisfactory partial reversal is likely to be obtained with low dose vitamin K (at one-tenth of the therapeutic dose) given parenterally (Bolton-Maggs & Brook, 2002) or orally, although the data for this route are known only for adults (Crowther et al., 1998).
- The INR should be checked after 2 to 6 hours, and further doses given as required.
- If a high INR is associated with bleeding immediate reversal can be obtained with FFP (pathogen inactivated) or theoretically with a factor IX concentrate ('PCC') containing factors II, IX and X (factor VII may be required in addition). However, there are no published data in children.

Children on oral anticoagulants may require dental extractions. Evidence in adults demonstrates that extractions may be safely carried out without stopping the anticoagulation providing the INR is within the therapeutic range and there is no gross gum pathology (Devani, Lavery, & Howell, 1998: **level IIa evidence**). Good local haemostatic modalities are sufficient under these circumstances (Saour et al., 1994; Blinder et al., 1999: **level IIa evidence, grade B recommendation**).

Autologous Transfusion in Children

Indications and Aims

As in adult practice, autologous transfusion techniques are employed primarily with the intention of reducing allogeneic donor exposure.

Autologous predeposit should be considered for children undergoing elective surgical procedures, including bone marrow harvest, in which there is a reasonable expectation that blood will be transfused.

Normovolaemic haemodilution and red cell salvage may be useful as an alternative or an adjunct to autologous predonation to minimize red cell losses during surgery. These techniques are not addressed further here but details can be found in the Guidelines of the British Committee for Standards in Haematology (1993). The potential adverse effects of these procedures should be taken into account in discussing the options with the child and/or parents. Patients who predonate autologous blood are more likely than others to receive a transfusion as they are more likely to be anaemic at the time of surgery and tend to be transfused with their autologous units at a higher haematocrit.

The child must understand the nature of the procedure and be willing to co-operate. Informed consent must be obtained from the parents.

Autologous Predeposit

- This should be considered in children over 25 kg but is technically difficult below this weight.
- The iron status of the child should be considered.
- Children with no unstable cardiovascular or pulmonary problems and a Hb concentration of >11 g/dL can be considered for predeposit.
- The maximum volume drawn at each donation is 12% of the estimated blood volume. The volume of citrate anticoagulant in the pack should be adjusted as required to maintain the appropriate ratio of blood to anticoagulant.
- Packs for paediatric use, which contain 35 mL of anticoagulant for the withdrawal of 250 mL of blood, are available and should be used wherever possible. Packs with small gauge needles suitable for phlebotomy in children should be used, when available.
- In some children a 'leap-frog' technique has been used to ensure a more adequate collection of blood. In this, the oldest donation that has been collected is re-infused during the collection of a 'double-volume' unit to avoid excessive volume depletion and acute anaemia.
- It should be borne in mind that this exposes the child both to the risks of the donation and to the risk of transfusion. The transfusion of an autologous unit, while not carrying a risk of viral transmission (unless units have been mixed up) may still result in a potentially fatal septic transfusion reaction (Popovsky, Whitaker, & Arnold, 1995). If the predeposited blood is not used, it may be appropriate to give supplemental iron for a few weeks.

Blood Handling and Administration

The serious hazards of transfusion reporting scheme (Love et al., 2001; Stainsby et al., 2003) has shown that children as well as adults may be affected by transfusion errors, may suffer from immunological transfusion reactions and may develop transfusion-transmitted infections. There are a number of circumstances that may place infants and children at particular risk.

- Confusion of maternal and baby (or placental) samples at time of birth, perhaps because of prelabelling of sample tubes or failure to label a sample from the mother before drawing the placental sample.
- Newborn multiple births. Mistakes may occur due to transposition of samples, for example, due to placental sampling with allocation of the wrong placenta to a particular baby or due to confusion arising between laboratory and neonatal unit when the infants are finally named.
- Failure to apply wristbands, particularly in children who are too young to state their identity and date of birth.
- Failure to communicate special transfusion needs during shared care. The particular risks facing patients who require irradiated products may be minimized by the issue of a special card recently developed by the British

Committee for Standards in Haematology in collaboration with the National Blood Service Clinical Policies Group.

For these reasons, attention to the correct identification of the patient and product at all stages of the transfusion process is essential. Monitoring during transfusion is equally necessary in paediatric patients as in adults and perhaps more so in younger children who may be less able to communicate discomfort or anxiety (British Committee for Standards in Haematology, 1999).

Definitions:

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials.

Ib Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of Recommendations

Grade A Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib).

Grade B Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels IIa, IIb, III).

Grade C Requires evidence obtained from the expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window]

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Reduced infant and child morbidity and mortality from blood or blood component transfusions

POTENTIAL HARMS

- Exchange transfusion is a specialist procedure associated with a potential for serious adverse events. As such, it should be undertaken only by staff who are experienced in the procedure.
- Transfusion errors, immunological transfusion reactions, and transfusion-transmitted infections are potential hazards of transfusion.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Although the advice and information contained in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have been made.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Boulton F, BCSH Transfusion Task Force. Amendments and corrections to the 'transfusion guidelines for neonates and older children'. London (UK): British Committee for Standards in Haematology (BCSH); 2005 Dec 7. 5 p. [9 references]

Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P, Burbin G, Duguid J, Boulton F, Cohen H, Smith N, McClelland DB, Rowley M, Turner G, British Committee for Standards in Haematology Transfusion Task Force: Writing Group. Transfusion guidelines for neonates and older children. Br J Haematol 2004 Feb;124(4):433-53. [113 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Feb (addendum released 2005 Dec)

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

British Committee for Standards in Haematology Transfusion Task Force

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

2004 Guideline

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

2005 Addendum

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Addendum 1 to transfusion guidelines for neonates and older children. 2007. 1 p.

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on May 23, 2008. This summary was updated by ECRI Institute on August 1, 2008. The updated information was verified by the guideline developer on September 1, 2008.

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Date Modified: 10/27/2008